ever over its American representatives. Any difference which may possibly exist between the two Veratrums is in favor of the American drug as less apt to disturb intestinal digestion. Under such circumstances the recognition by the *United States Pharmacopœia* of the European drug seems to us of doubtful expediency.

CRITICAL SUMMARY

OF THE

QUESTION OF FATTY DEGENERATION.

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THE question of fatty degeneration, so called, is entangled in the question of the relations of the nitrogenous to the carbonous metabolism as exemplified in the carbohydrates and hydrocarbons. We need to know the following in connection with the processes known as fat metamorphoses: What are these fats? Do they differ from the physiological fats? Whence are they derived? These questions presuppose a knowledge of the physiological fats, their origin, and their uses, and to a certain extent the pathological questions await the solution of the physiological questions. In theory, however, the interdependence need not be complete; even were it shown that physiologically fats are or are not produced from proteids, the contrary would still be possible under pathological conditions. The same holds true for comparative studies; the formation of fat in plants need in no wise correspond to the procedure in animals. Nevertheless, biological reasoning by analogy is of great value, and in the study of fatty degeneration we are largely thrown upon such studies, since direct investigations in connection with diseases are very difficult to institute, and are attended by almost countless opportunities for error and fallacy.

The current pathological teaching is that in fatty degeneration the proteids of the diseased cells become converted into fats. Virchow and Klebs are largely responsible for this, and Klebs's ideas and work were chiefly based upon those of the elder Voit. In general pathological literature no explanation or discussion of worth attends the statement quoted. For this serious error of thus dismissing with an unequivocal statement one of the most fundamental problems of biology there is no excuse, and it constitutes a most flagrant violation of pedagogic principles.

Fats may be conceived as derived either from fats, from carbohydrates, or from proteids. We know that fats may be absorbed as such, unchanged. We know that in the process of digestion fats are usually broken up into their respective acids, which combine with bases; from these compounds, after their absorption, fats are re-formed. All fats seem to be absorbed by the lymphatic apparatus. Once in the body they are stored for immediate or future use. In the process of calorification they are probably burned as such. So far as we know fats are never formed from glycogen or glucosides; glycogen is converted into sugar, and from this fats may undoubtedly be formed. To what extent they are thus formed from sugar we do not know. For example, a person is upon a diet which contains a sufficient quantity of proteid and an excess of carbohydrates and fats; he lays on flesh, but we do not know whether he burns his sugars and deposits the ingested fats, or whether he burns his fats to a certain extent and converts the excess of the sugars into fats and deposits them. As a principle of economic mechanism it is natural to suppose that the sugars would be burned and the fats deposited, but we have no right to assume that all physiological processes are in conformity to the laws of economical mechanics. The relations of the fats to the sugars are of subsidiary importance in the question under discussion; our chief concern is with the relations of the fats to the proteids.

There are obviously three avenues by which this problem may be approached. The first is by the experimental study of various diets and their effects upon the metabolism; the second is by a study of the body fats; the third is by the experimental production of fatty degeneration and the processes which attend them. Obviously these may be combined, the last two with especial advantage. In considering the experiments which have been carried out in these connections, it must not be forgotten that analogies drawn from synthetical laboratory work cannot be rigidly applied to these questions. It is probably true that under the influence of mineral acids and high temperatures carbohydrates may be produced from proteids; it is probably true that lactic, valerianic, and butyric acids may be made from proteids, and that from lactates fatty acids may be derived by the action of alkalies or high temperatures; and it is true that some bacteria form fatty acids and fat from nitrogenous substances, as in the ripening of cheese; but all of these do not prove or even indicate that such processes take place within the living body. Urea may be easily formed from cyanides; it is not so derived in actual life. There has been a great deal written upon fatty degeneration, but there has been little work done. No attempt is made in this summary to review anything but original work directly bearing upon the problem.

The earliest direct experimental work was done by Hoppe[1] (Hoppe-

Seyler). He fed a dog first on sugar, and then on meat and sugar, and found that more CO_2 was eliminated upon the meat-and-sugar-diet than upon the sugar-diet, while on the mixed diet less urea was passed. Since the gain in weight was more marked upon the mixed-diet than upon the sugar-diet, he concluded that some of the fat was formed from the meat of the diet. He conceded that his calculations were not exact, and overlooked entirely the fact that an increase in weight might not have been due to fat at all, but to water. The experiment proved nothing, but simply illustrated that carbohydrates enabled the body to economize upon its nitrogenous metabolism.

C. Voit[2] then took up the question, and the Munich school has since produced the sponsors of proteids as sources of fats. Their experiments were partly dietetic and partly metabolic, consisting of total nitrogen and carbon estimations. They fed dogs upon a known quantity of meat, and then determined the quantities of nitrogen and carbon eliminated. They found all the nitrogen passed out, but a part of the carbon (14 to 18 per cent.) was retained. This retention they considered to have been in the form of fat, the process being that the molecule of albumin was broken up into a nitrogenous and a non-nitrogenous moiety; the nitrogenous moiety was broken up and appeared largely as urea, while the non-nitrogenous moiety, instead of being oxidized to CO_2 and H_2O, was retained as fat. They conceived nearly all the body-fats as derived from the proteids, directly or indirectly; even in herbivora they did not think carbohydrates were to any extent converted into fats. The process from proteids to fats they represented as a reduction which caused a consumption of energy; the formation of glycogen from proteids, however, was a simple oxidation. Thus the actual *modus operandi* of the formation of fats from proteids was never explained by them. Voit constantly quoted the fatty degenerations, phosphorus poisoning, and the adipoceration of ripening cheese in support of his view, and did not seem conscious of the fact that by so doing he was attempting to prove each by the other. The work of Voit and his students, on the one hand, and the weight of the current pathological teaching upon the other, seemed to settle the matter, and for twenty years little work was done in relation to it. Liebig objected that the meat used in their diets was not fat-free, but without effect.

In the course of a life's work upon the sources of muscular energy Pflueger reached general ideas which did not harmonize with those of Voit. He therefore took up the matter, and in several articles[3] criticised in detail the theory of the formation of fats from proteids. He demonstrated (what has later been admitted by students of Voit[4 5]) that the coefficient employed by Voit was incorrect, being too high. Voit had fed his animals on meat which he had not analyzed, but calculated on the basis of now admittedly incorrect analyses. He assumed that his meat contained 3.4 per cent. of nitrogen, which was probably too low, and in any event was not accurate. This amounted to 14.11 per cent. of nitrogen in the dried residue, but a fluctuation would result from the inconstancy of the water. He assumed that the carbon was 51.95 per cent. of the dried residue, which was higher than current figures; it may have been too high, in any event was not derived by analysis. The coefficient derived from the relation of nitrogen to carbon was therefore too high, because he had used a low figure for nitrogen and a high figure for carbon. Voit's calculations also obviously assumed that all the nitrogen and carbon of meat were in the form of proteid; they are not, and the more non-proteid nitrogen there was the greater would be the proportionate reduction of the meat, since these substances were eliminated almost unchanged. We know the muscles contain some more glycogen and glucosides and a great deal more fat than Voit supposed; since these might not have been oxidized but stored, they alone would have given a carbon retention. When Voit's figures are recalculated with the correct coefficient the carbon retention disappears. Even though the fat formation (carbon retention) he described had occurred, it might still have been due to the fat and glycogen in the diet he employed. Pflueger also pointed out that although there was in Voit's figures a urinary nitrogen balance, there was at the same time a marked increase in weight, which was contrary to his wide experience with pure meat diets. This, therefore, confirmed the fact that Voit had judged the nitrogen in his diet too low, and that the animals had retained nitrogen as well as carbon. Other questionable factors in Voit's work were the paucity of water given to the animals, the method employed (Liebeg's) for the determination of the urea and the irregular fluctuations in it, and his results in the estimation of the feces, and of oxygen in the respiration apparatus. It is clear that these experiments of Voit's in nowise proved a derivation of fats from proteids.

E. Voit repeated the experiments, and in his calculations employed a lower coefficient—3.29. He admitted that in the earlier experiments of C. Voit it was an error not to have analyzed the meat and to have inferred from a gain in weight a gain in fat. He fed a dog with washed meat and some albumin; the experiment lasted three days, and was apparently not preceded by starving, nor were the stools stated to have been marked off. The meat was not analyzed for fats or glycogen. He found a slight nitrogen retention and a larger carbon retention, which he attributed to fat formation and not to glycogen formation, "because that was not probable." Our more recent knowledge of the fats and glycogen in muscles have still further reduced the carbon-nitrogen coefficient, so that E. Voit's figure was still much too high. The assumption that the carbon was retained in the form of a fat was by no means obvious; as Pflueger[5] showed, substances which arise during the reduction of the proteid molecule, as tyrosin, could well have accounted for it. The essential difference between these experiments and the older ones of C. Voit lay in the fact that while C. Voit noted only a carbon retention, E. Voit noted both a nitrogen and a carbon retention. Therefore, it was all the more necessary to show that the retentions were in the form of fat and not in the form of other substances, particularly as the diet in these experiments was abnormally heavy in proteids. That demonstration E. Voit did not give.

Cremer[6] took up the subject in the same line as E. Voit. He overfed starved cats on meats, and stated that about 17 per cent. of the carbon of the meat was retained in the form of fats. He stated that his meat was free from fat and glycogen, but did not state how he knew it was so, nor how he obtained it so. He fed his cats three times the normal diet for eight days, but did not determine how much lay in the digestive tract at the end of the experiment. About 12 per cent. of the nitrogen and about 27 per cent. of the carbon were retained. In the digestive tract of a cat on a meat diet putrefactive processes are active, but fermentative processes are inactive. Of any of the excessive diet retained in the tract, the proteids would have been broken up into highly nitrogenous substances, as ammonia and extractives, which, being easily absorbed, would have entered the blood and been eliminated by the kidneys; in the meanwhile the carbonous substances of the proteids would have remained in the tract, and would in the calculations have been incorrectly credited to fats in the body; a retention and putrefaction of 10 per cent. would more than have accounted for the results. Another error lay in the use of beef, since it was obviously calculated that the beef and the tissue the cat formed from it were of identical composition; obviously the difference should have been determined and allowed for, or cat's meat employed in the diet. And, lastly, Cremer failed entirely to demonstrate that the carbon held to have been retained was retained as fat or glycogen, and not in substances in combination with the nitrogen, which was also retained. There is no doubt that Pflueger's criticisms[5] of this work have shown its entire unreliability. It is clear that not only has it never been shown in diet experiments that fats are directly or indirectly formed from proteids, but it is certain that no decision can be reached in this way unless a pure proteid is employed as the diet, and even then all the inherent difficulties of the method will not have been overcome.

The direct study of the fat metabolism has given more definite results. Subbotin[7] fed dogs, made thin by starvation, on pure meat with isolated forms of fat; one had meat with palmin, another with an olein-free soap. He found stearin and olein in the body-fats, and concluded that these must have come from the proteids of the diet, since the dog and the diet were supposed to have been free of fat and glycogen except for the palmin and olein ingested. These experiments simply proved that the dog could re-form its own type of mixed fat from palmin or olein. In all probability the dog was not freed of its carbohydrates by the starvation, and the period was not long enough to have freed the body of its stored-up fats; nor could the diet, according to our present knowledge, have been assumed to have been even approximately free of fat and glycogen. Munk,[8] in addition, was able to show an error in Subbotin's work, and that palmin, as such, was deposited by the dog, so that the experiment proved nothing for fat-formation.

Subbotin[9] stated that the milk of bitches fed on a meat diet was richer in fats than when the animals were fed on a mixed diet. Voit[3] made the same statement, and Kemmerich[10] stated that the fat in the milk might exceed the fats (not fats and carbohydrates) in the diet. Voit himself admitted that against the interpretation of these facts as proofs of a formation of fats from proteids would be the obvious objection that the milk-fats could have come from the body-fats; this he declared improbable, but made no attempts to disprove it. The later work of Rosenfeld has nullified Voit's interpretation.

Radziejewski[11] fed a lean dog on meat and seal-oil, but was not able to demonstrate in the body the erucin of the seal-oil. Munk[8] repeated the studies, and was able to show that erucin was in the tissues—*i. e.*, that the seal-oil had been absorbed unchanged. Subbotin[7] tried the experiment with spermaceti, but failed. Lebedeff[12] fed a lean dog on mutton-fat and linseed oil, and was able to find both in the tissues. He also[13] fed a lean dog for ten days on meat and linseed oil, then poisoned the dog with phosphorous and killed it on the fourth day; the phosphorous liver was full of fat, and of this two-thirds was linseed oil. The objection that the oil might simply have been lodged in the liver could not hold, for it is known that the fats are not absorbed through the portal circulation. In other experiments he likewise found that foreign fats were deposited in the liver.

Rosenfeld[14] has demonstrated that when dogs were starved and then fed on mutton-suet they absorbed and deposited this fat unchanged, and it was conclusively demonstrated as such in the tissues. When these animals were again starved the fats disappeared from the liver. Then the animals were given phloridzin; there was a marked fatty change in the liver; this fat was mutton-fat, which had been transferred from other tissues to the liver, and was not formed there; the liver in the meantime has lost but little of its nitrogen. The same experiments were repeated with phosphorous poisoning, and again it was shown that the fat in the liver was mutton-fat, which had been stored from the diet, and not dog-fat at all. He also showed that badly starved fowls did not present a fatty liver after phosphorous poisoning, while fowls in good nutrition did so. Rosenfeld finally applied his method of study to the milk, the classical example of the formation of fats from proteids. He starved a bitch and then fattened her with mutton-suet. She was then impregnated, and during gestation was fed on lean beef. She aborted, but presented a good secretion of milk. The fat in this milk was mutton-fat. Thus Rosenfeld proved that in poisoning by phloridzin and phosphorous and in the milk of animals subjected to a previous fattening with mutton-fat, the fat was not derived from the proteids, but from the body-fats; the process was an infiltration, and not a degeneration. These experiments have refuted nearly all the older views on fatty degeneration to which Voit used to appeal for support.

Bauer[15] had analyzed isolated pieces of tissues of animals with phosphorous poisoning and found them to contain more fat than the normal tissues. Since Storch,[16] Schultheissen and Riess,[17] and Fränkel[18] showed that the urea was increased in connection with phosphorous poisoning the inference lay close at hand that the fats had been formed from the disintegrated proteids. In fact, the inference was an assumption. It did not follow at all that because the urea was increased that only the nitrogenous and not the carbonous moiety of the proteid was destroyed. Analyses of small pieces of tissue could not prove whether the fat in the whole body was increased or not, since the water, the salts, the glycogen, and the conditions of metabolism at the time of death can and constantly do produce such individual variations that from such analyses almost any postulate could have been supported. Furthermore, the fat in local areas could have been an infiltration; and in any event the fat metabolism may have been decreased in phosphorous poisoning, which, in connection with the exaggerated proteid disintegration, would have produced a deceptive appearance of fat production. Saikowsky[19] showed that the phosphorous liver was almost free from glycogen, from which a notable quantity of fat could have been derived.

Monaco[20] studied the metabolism of mice poisoned with phosphorous, and was able to show that the respiratory exchange was not decreased, and that the urinary nitrogen was but little increased. These results were in direct contradiction to those of Bauer.

It is obvious that, apart from such experiments as those of Rosenfeld, the fat metabolism of phosphorous poisoning can be well studied only in small animals which can be analyzed entire at the close of the experiments. It would obviously be of further advantage to utilize such animals as can be starved (since it is practically impossible to use a proteid diet and sugar-free diet) without detriment to their metabolism, as hibernating animals. The first of these desiderata seems to have originally occurred to Leo.[21] His experiments were divided into three series. In the first series he took young guinea-pigs, and, after weighing them, after a five days' starvation poisoned one with phosphorous; both were killed on the third day. The poisoned pig contained much more of matters extractable by ether than did the unpoisoned pig. In the second series he starved two rats, of similar litters, size, and rations for five days, and poisoned one with phosphorous; he killed them on the fourth day, and found, on analyses, that the poisoned rat contained less substance extractable in ether than did the unpoisoned animal. In the third series he used frogs, which were divided into three groups of six each. The poisoned frogs showed a larger amount of matters extractable in ether than did the unpoisoned frogs. From these studies Leo concluded that fat was produced from proteids in phosphorous poisoning; the contrary results in the experiments with the rats he explained by assuming that there had been an excessive combustion of fats, for which there was no proof. There were many apparent fallacies in Leo's work. He did not determine the fats, but only the total substance extractable in ether—a method of fat estimation which has no standing to-day, since many other substances—cholesterin, pigments, etc.—were included. He did not employ animals of the same sex, which was especially essential in frogs, in which he obtained his most striking results. He did not employ animals of equal weight. He made no attempt to exclude other substances, as glycogen, from which the fat might have been derived. Hoppe-Seyler[1] had in his work expressed the idea that it was from the lecethins that fats were indirectly derived from proteids; in this work Leo found the lecethins not increased, thus disproving Hoppe-Seyler's view.

Schmidt[22] made similar experiments on young pigeons of similar age, size, and rations. All were starved through the period of experimentation, two were poisoned with phosphorous. He found rather less fat in the poisoned than in the unpoisoned animals.

The publication of Bergeat[23] contained the positive statement that he has been able to demonstrate the formation of fat from proteid in rats poisoned by phosphorous. He gave no details of methods nor protocol of results, and his statements cannot therefore be discussed or considered.

Polimanti[24] next took up the matter. He found that male and female frogs have widely different quantities of fat. He therefore selected male frogs, which possess the least fat, removed the fatty bodies by operation, and then divided the animals into two groups and submitted one group to phosphorous poisoning. He found that the poisoned animals contained more fat than the unpoisoned. Since the animals had had no food, and assuming that they did not contain enough glycogen to account for the increase in fat, he concluded that fat had been formed from proteids.

Polimanti's procedures included several errors which Pflueger[25] pointed out. He had weighed his frogs when dead, and not at the beginning of the experiments. Obviously he assumed that during an eight-day course of phosphorous poisoning the weight of the frogs remained constant, and that of this weight the solid constituents remained the same. This we know cannot have been true, since phosphorous poisoning produces an increase of metabolic disintegration, as evidenced by the increase of urea passed. Therefore, since the frogs lost solid matters, a higher percentage of fat in the dried residue might simply have corresponded to this loss, and not have represented a gain in fat at all, since the fats were not disintegrated to the same extent as were the proteids. What we need to know is the relation of the fats to the weight of the healthy frogs before the poisoning. He used larger frogs for his experiments and smaller frogs for his controls, which vitiated the results, since we know that as a rule larger animals have a higher percentage of fat than the smaller. Pflueger showed by careful analyses that frogs contained more glycogen than was necessary to account for the apparent (not real) increase in fat in Polimanti's frogs, and thus robbed his conclusions of their validity. It is now clear that the question can be decided by selecting frogs of the same kind, sex, and size, poisoning a part of them, and then comparing in the two series the quantity of fat, glycogen, and proteid (nitrogen) of the entire series with the live weight before the experimentation. This has not yet been done, and the demonstration of the origin of fats from proteids in phosphorized animals has not yet been produced, while against it stand the clear results of Rosenfeld.

A few other aspects of the question deserve a moment's notice. Hoffman[26] took the eggs of musca vomitoria and divided the quantity in halves. One portion he analyzed for fats; the other portion he allowed to hatch out upon a blood of a low and known fat and sugar content. When the insects were grown he analyzed them, and found that they contained ten times as much fat as did the original eggs. This fat, he concluded, must have been made from the proteids. As Pflueger[3] pointed out, however, this fat was probably formed by bacteria and then taken up by the insects. We know that in the ripening of cheese, in the putrefaction of proteids, and in the condition known as adipocere, large quantities of fat and fatty acids are formed by bacterial action. This explanation, in all probability, holds for the experiments of Hoffman.

As for the fatty changes in the dead extra-uterine fœtus, long held to have been due to a metamorphosis, we now know that it is an infiltration, just as the lime-salts in the lithopædion are an infiltration. The work of Reinhard[27] and Virchow[28] on the formation of cholesterin did not prove much at the time, and has been entirely destroyed as evidence in this matter by the work of Rosenfeld. The later statement of Virchow, that chemistry alone, and not microscopy, could decide the question of fatty degeneration, holds true to-day.

The position and appearance of fat granules within degenerated cells proves nothing for the origin of the fats. Even though it were conceded that the fat was formed within the cell, it could more probably have been formed from the carbonous compounds—sugar, glycogen, glucosides, and mucin, which abound in cells—than from the proteids. It is especially in the muscle, liver, and epithelium that fatty degenerations are most marked, and it is in them that the carbonous substances are most abundant.

It has long been known that when porous foreign bodies are placed in the living body, as in the lymphatic spaces, fatty degenerations may occur in the cells which have wandered in, and this has been looked upon as a good illustration of fatty metamorphosis. Apart from the fact that leucocytes contain glycogen which might have been the origin of the fat, what we know now of the pith experiment through the work of Arnold and others forces us to conclude that the fats are deposited by wandering cells and do not originate in the cells within the foreign bodies.

A careful review of the subject thus leads us to the following conclusions: 1. The formation of fats out of the proteids physiologically has not been demonstrated or made probable. 2. A formation of fats out of proteids pathologically has not been demonstrated. On the contrary, the weight of evidence is against it and in favor of the conception of the so-called fatty metamorphosis as infiltrations or formations of fat from carbohydrates. This position is provisional, and not conclusive. No one pretends to-day that the formation of fat from proteids is impossible; it has simply not been demonstrated or even made plausible. Future work must confirm or reverse our present conclusions.

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